EXHIBIT D

PATENT

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE
BEFORE THE BOARD OF PATENT APPEALS AND INTERFERENCES

In re Application of: Philip E. Thorpe and Rolf A. Brekken	Group Art Unit: 1642
Serial No.: 09/561,005	Examiner: Yaen, C.
Filed: April 28, 2000	Atty. Dkt. No.: 3999.002585
For: ANTIBODY CONJUGATE METHODS FOR SELECTIVELY INHIBITING VEGF	

BRIEF ON APPEAL

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37 C.F.R. § 1.8

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BRIEF ON APPEAL

Sir:

Appellants hereby submit an original and two copies of this Appeal Brief to the Board of Patent Appeals and Interferences in response to the Second and Final Official Action dated April 23, 2002. The Notice of Appeal was submitted on October 23, 2002, and was received in the Office on October 29, 2002. The two month date for filing the Appeal Brief was December 29, 2002 and the Brief is timely filed within the extendable period thereafter. The large entity fee for filing this Appeal Brief is $320, which is enclosed herewith.

If the check is inadvertently omitted, or should any additional fees under 37 C.F.R. §§ 1.16 to 1.21 be required for any reason relating to the enclosed materials, or should an overpayment be included herein, the Assistant Commissioner is authorized to deduct or credit said fees from or to Williams, Morgan & Amerson, P.C. Deposit Account No. 50-0786/3999.002585.

I. REAL PARTY IN INTEREST

The real parties in interest are the Assignee of the application, Board of Regents, The University of Texas System, and the exclusive licensee, Peregrine Pharmaceuticals, Inc.

II. RELATED APPEALS AND INTERFERENCES

An Appeal Brief was filed in related Application Serial No. 09/561,108 ("the '108 application"), after which all claims were allowed without amendment. The application issued as U.S. Patent No. 6,342,221 ("the '221 patent"). A copy of the Appeal Brief has been made of record in the present application.

III. STATUS OF THE CLAIMS

Claims 1-46 were filed with the original application. In a Restriction Requirement dated July 05, 2001, the original claims were said to be drawn to nine distinct inventions. In a response submitted July 30, 2001, Appellants traversed the Restriction Requirement, suggested clarification thereof and amended claims 1, 2 18 and 35.

The first Official Action dated October 26, 2001 maintained the Restriction Requirement and examined claims 5-23, 29, 30 and 42-45 on the merits. The first Official Action rejected claims 5-23, 29, 30 and 42-45 under 35 U.S.C. § 112, first paragraph and rejected the same claims under 35 U.S.C. § 112, second paragraph. In a response submitted January 15, 2002, Appellants added claims 47-54, which were entered and examined on the merits.

The second Official Action ("final Action") dated April 23, 2002 finally rejected claims 5-23, 29, 30, 42-45 and 47-54 under 35 U.S.C. § 112, first paragraph and 35 U.S.C. § 112, second paragraph.

On July 11, 2002, Appellants submitted a response under 37 C.F.R. § 1.116. No claims were amended, canceled or added. An Advisory Action has yet to be mailed. Claims 1-54 are therefore pending; claims 1-4, 24-28, 31-41 and 46 have yet to receive an examination on the merits; and claims 5-23, 29, 30, 42-45 and 47-54 are finally rejected and appealed.

IV. STATUS OF AMENDMENTS

Claims 1-54 were pending at the time of the final Action. Claims 5-23, 29, 30, 42-45 and 47-54 have been examined on the merits and are subject to final rejection. Appellants maintain their traversal of the Restriction Requirement and their position that claims 1-4, 24-28, 31-41 and 46 are not patentably distinct from claims 5-23, 29, 30, 42-45 and 47-54.

No amendments have been sought subsequent to the final rejection. Claims 5-23, 29, 30, 42-45 and 47-54 are pending, finally rejected and are the subject of this appeal. The claims on appeal are set forth in **Appendix A**.

V. SUMMARY OF THE INVENTION

The present invention relates to the field of cancer treatment, and provides methods for treating animals with primary and metastatic tumors using antibody-based therapeutic agents termed "immunoconjugates". The immunoconjugates for use in the claimed methods comprise an antibody or antibody binding region, which imparts a specific targeting property, attached to a therapeutic agent selected for its particular biological and therapeutic properties. The antibody components of the immunoconjugates bind to VEGF (vascular endothelial growth factor) with defined epitope specificity and have improved safety over other antibodies against VEGF due to their specific blocking properties (specification at page 4, lines 6-13).

The invention particularly provides methods for treating an animal having a vascularized solid tumor (claims 5 and 49), a metastatic tumor (claims 5 and 50) or metastases from a primary tumor (claims 5 and 51), comprising administering to the animal a therapeutically effective amount of a pharmaceutical composition comprising at least a first immunoconjugate that comprises at least a first therapeutic agent operatively attached to at least a first anti-VEGF antibody, or antigen-binding fragment thereof, that "binds to substantially the same epitope" as the 2C3 monoclonal antibody, deposited as ATCC PTA 1595.

By binding to substantially the same epitope as the deposited 2C3 antibody (claims 5 and 49-51), the antibodies of the claimed immunoconjugates are able to effectively compete with 2C3 for binding to VEGF. The invention thus also provides methods for specifically delivering therapeutic agents to cells expressing the VEGF receptor termed VEGFR1 (claim 52), which

exist within vascularized tumors (claim 53), and methods for treating an animal having a vascularized solid tumor, a metastatic tumor or metastases from a primary tumor (claim 54), comprising administering to the animal a therapeutically effective amount of a pharmaceutical composition comprising an immunoconjugate in which the anti-VEGF antibody, or antigen-binding fragment thereof, "effectively competes" with the deposited 2C3 antibody for binding to VEGF (claims 52, 53 and 54).

The specific blocking properties of the antibody portions of the immunoconjugates provide particular advantageous in tumor treatment. As the antibodies and immunoconjugates specifically inhibit VEGF binding to only one of the two primary VEGF receptors, they are able to inhibit angiogenesis and induce tumor regression as effectively as other anti-VEGF antibodies, including those already in clinical trials, and yet have improved safety. The ability to significantly inhibit VEGF binding to the VEGF receptor VEGFR2, without significantly inhibiting VEGF binding to the VEGF receptor VEGFR1, allows the detrimental effects mediated by VEGFR2 to be inhibited, whilst maintaining the beneficial effects mediated by VEGFR1, thus providing clinical benefits in anti-tumor responses and bone metabolism (claims 43, 44 and 45; specification at pages 4-6).

The immunoconjugates for use in the methods of the invention may comprise various antibody species (claims 6-10), and any one or more of a number of exemplary therapeutic agents (claims 12-23), including cytotoxins (claims 14-16), anti-angiogenic agents (claims 17-19), anti-tubulin drugs (claims 20 and 21) and coagulants (claims 22 and 23). The immunoconjugates may be administered intravenously (claim 29), optionally as a liposomal formulation (claim 47), and the treatment method may be combined with radiotherapy (claim 30).

In certain embodiments, the antibody portion of the immunoconjugates "binds to the same epitope as the monoclonal antibody 2C3 (ATCC PTA 1595)" (claim 48), and methods of using the deposited 2C3 antibody itself are recited in claim 11.

The claims as a whole therefore define methods of treating cancer by administering immunoconjugates in which the antibody portions bind to the same or substantially the same epitope as the deposited 2C3 antibody and thus have "defined epitope-specificity" (specification at page 13, lines 15-20). The antibodies of the immunoconjugates in the claimed methods thus have immunospecificity for substantially the same epitopic site as 2C3, meaning that the antibodies are able to effectively compete with 2C3 for binding to VEGF, as defined in routine antibody competition assays (specification at page 14, lines 19-27).

VI. ISSUES ON APPEAL

A. Whether, in regard to the recitation of tumor treatment, claims 5-23, 29, 30, 42-45 and 47-54 particularly point out and distinctly claim the invention in accordance with 35 U.S.C. § 112, second paragraph;

B. Whether, in regard to the recitation of binding to substantially the same epitope and effectively competing, claims 5-23, 29, 30, 42-45 and 47-54 particularly point out and distinctly claim the invention in accordance with 35 U.S.C. § 112, second paragraph; and

C. Whether, in regard to the recitation of binding to substantially the same epitope and effectively competing, claims 5-23, 29, 30, 42-45 and 47-54 are supported by an enabling specification in accordance with 35 U.S.C. § 112, first paragraph.

VII. GROUPING OF THE CLAIMS

Many claims stand or fall separately according to the issues on appeal. Appellants group the claims as follows, for the stated reasons:

A. For rejection under 35 U.S.C. § 112, second paragraph regarding tumor treatment, claims 43-45 and 49-53 stand separate from all other rejected claims as they either separately recite the rejected terms (claims 43, 44, 45, 49, 50, 51 and 53) or do not contain the language subject to rejection (claim 52);

B. For rejection under 35 U.S.C. § 112, second paragraph regarding binding to substantially the same epitope and effectively competing, claims 11, 43-45, 48 and 52-54 stand separate from all other rejected claims as they either do not contain the rejected terms (claims 11 and 48), separately recite the rejected terms (claims 52, 53 and 54) or contain additional language that further defines the meets and bounds of the invention (claims 43, 44 and 45); and

C. For rejection under 35 U.S.C. § 112, first paragraph, claims 11, 43-45, 48 and 52-54 stand separate from all other rejected claims as they either do not contain the rejected terms (claims 11 and 48), separately recite the rejected terms (claims 52, 53 and 54) or contain additional language that is further enabled by the specification (claims 43, 44 and 45).

For the sake of clarity, Appellants' grouping of the claims in this manner is brought out in the argument specifically addressing each rejection.

VIII. ARGUMENT

A. Claims 5-23, 29, 30, 42-45 and 47-54 are Definite Under 35 U.S.C. § 112, Second Paragraph in Regard to Tumor Treatment

The Office rejects claims 5-23, 29, 30, 42-45 and 47-54 under 35 U.S.C. § 112, second paragraph on the basis that the differences between "metastatic tumor, metastasis from a primary tumor, and a vascularized solid tumor" in claim 5 are not clear (first Action at item 5A; final Action at Item 3, first and second paragraphs).

Claim 52 is immune to this rejection, as this claim is directed to a method of specifically delivering a therapeutic agent to a VEGFR1-expressing cell, and does not contain any of the terms "metastatic tumor", "metastasis from a primary tumor" or "vascularized solid tumor".

Claims 43, 44, 45, 49, 50, 51 and 53 are also free from this rejection as these claims separately recite only one of the three terms included in the alternative in claim 5. In particular, claims 43, 44, 45, 49 and 53, are directed to the treatment of "vascularized solid tumors and "vascularized tumors", whereas claim 50 is directed to the treatment of "a metastatic tumor" and claim 51 is directed to the treatment of "metastases from a primary tumor". As the rejection is

based upon the inclusion the three terms within a single claim, it is inapplicable to claims 43, 44, 45, 49, 50, 51 and 53.

As to claims 5-23, 29, 30, 42, 47, 48 and 54, the rejection is overcome as one of ordinary skill in the art would readily understand the meets and bounds of these claims in light of the present specification and the knowledge in the art.

Each of the terms "metastatic tumor", "metastasis from a primary tumor" and "vascularized solid tumor", as used individually, are well understood in the art (*Cancer: Principles & Practice of Oncology, 6th Edition,* Chapter 8 and Chapter 9; **Exhibit A**). A vascularized solid tumor can exist that is not metastatic (**Exhibit A**, page 125, column 2); however, vascularized primary tumors do often become metastatic (**Exhibit A**, page 124, column 1), giving rise to metastatic foci, which often continue to grow (**Exhibit A**, page 125, column 1).

Appellants have not shown any intent to deviate from the ordinary and accustomed meanings of the recited terms. The claims are therefore sufficiently definite. "Claim terms take on their ordinary and accustomed meanings unless the patentee demonstrated an intent to deviate from the ordinary and accustomed meaning of a claim term by redefining the term or by characterizing the invention in the intrinsic record using words or expressions of manifest exclusion or restriction, representing a clear disavowal of claim scope". *Teleflex Inc. v. Ficosa North America Corp.*, 63 USPQ2d 1374, 1382 (Fed. Cir. 2002).

As to the use of these terms in the alternative, Appellants have the right to restate their invention in a reasonable number of ways, optionally by plural claiming. MPEP 706.03(k). There is nothing in claim 5 to signify lack of clarity or enablement[1].

For the foregoing reasoning, the first rejection under 35 U.S.C. § 112, second paragraph is in error and should be reversed.

B. Claims 5-23, 29, 30, 42-45 and 47-54 are Definite Under 35 U.S.C. § 112, Second Paragraph in Regard to Substantially the Same Epitope and Effectively Competing

Claims 5-23, 29, 30, 42-45 and 47-51 are rejected under 35 U.S.C. § 112, second paragraph on the ground that "substantially the same epitope" renders the metes and bounds of the claims unclear (first Action at Item 5B; final Action at Item 3, bridging pages 2 and 3). Claims 52-54 are also finally rejected under 35 U.S.C. § 112, second paragraph on the basis that the recitation "effectively competes with" renders the metes and bounds of the claims unclear (final Action at Item 3, page 3).

Even considering both aspects of this rejection together, claims 11 and 48 are *prima facie* free from this rejection. In claim 48, neither "substantially the same epitope" nor "effectively competes with" are present; and in claim 11, the "substantially the same epitope" language is read out of this dependent claim by the positive recitation of *the* deposited antibody.

As to the rejection of claims 5-10, 12-23, 29, 30, 42-45, 47 and 49-51, each aspect of the rejection is overcome as those of ordinary skill in the art would clearly understand the meets and bounds of these claims in light of the specification and the knowledge in the art.

[1]The Office suggests a non-Final Action to enter a new ground of rejection under 35 U.S.C. § 112, first paragraph, directed to a possible lack of enablement for the treatment of metastatic tumors and metastases from primary tumors, but not for the treatment of vascularized solid tumors. All claims are fully enabled as immunoconjugates against VEGF mediate both anti-vascular effects against established tumors and anti-angiogenic effects against established and metastatic tumors and metastases.

1. Counterpart Issued U.S. Patents

Appellants have twice pointed out that the recent issuance of the same claim language in counterpart applications[2] having the same specification is *prima facie* evidence of the clarity of the rejected terminology.

In the '221 patent[2,3], issued from the same specification, claim 1 defines the antibody portion of the immunoconjugates for use in the presently claimed methods as one that "binds to substantially the same epitope as the monoclonal antibody 2C3 produced by hybridoma ATCC PTA 1595", *i.e.*, using exactly the same language currently rejected as indefinite in claim 5 ('221 patent, claim 1; **Exhibit B**).

In U.S. Patent No. 6,342,219 ("the '219 patent")[3], issued from the same specification, claim 1 is directed to an antibody in accordance with the antibody portion of the immunoconjugates recited in the present claims. The antibody is defined as one that "binds to substantially the same epitope as the monoclonal antibody 2C3 produced by hybridoma ATCC PTA 1595", *i.e.*, again using the same language as currently rejected in claim 5 ('219 patent, claim 1; **Exhibit C**).

Claim 1 of U.S. Patent No. 6,416,758 ("the '758 patent")[3], issued from the same specification, defines the antibody portion of the immunoconjugates for use in the present methods as one that "effectively competes with the monoclonal antibody 2C3, produced by hybridoma ATCC PTA 1595, for binding to VEGF", *i.e.*, using exactly the same language currently rejected as indefinite in claims 52-54 ('758 patent, claim 1; **Exhibit D**).

Issuance of the '221, '219 and '758 patents, each using the same claim language as the present claims and having the same specification as the present application, compels a finding of

[2]Copies of three issued patents have already been made of record.
[3]A copy of the Appeal Brief from the first related patent has also been made of record in this case.

patentability for all rejected claims. 35 U.S.C. § 282; *Biovail Corp. International vs. Andrx Pharmaceuticals Inc.*, 57 USPQ2d 1813, 1816 (Fed. Cir. 2001).

2. Substantially the Same Epitope

The rejection based upon "substantially the same epitope" has been applied to claims 5-23, 29, 30, 42-45 and 47-51. Claims 11, 48 and 52-54 are free from this rejection, as they do not directly or indirectly include the rejected language. As to the rejection of claims 5-10, 12-23, 29, 30, 42-45, 47 and 49-51, aside from issuance of three U.S. patents with the same claim language, the record shows that the term "substantially the same epitope" is sufficiently definite.

The Federal Circuit has recently decided the latest in a long line of cases approving the use of the term "substantially" in patent claims:

> "Expressions such as 'substantially' are used in patent documents when warranted by the nature of the invention, in order to accommodate the minor variations that may be appropriate to secure the invention. Such usage may well satisfy the charge to 'particularly point out and distinctly claim' the invention, 35 U.S.C. §112, and indeed may be necessary in order to provide the inventor with the benefit of his invention. In *Andrew Corp. v. Gabriel Elecs. Inc.*, 847 F.2d 819, 821-22, 6 USPQ2d 2010, 2013 (Fed. Cir. 1988) the court explained that usages such as 'substantially' equal and 'closely approximate' may serve to describe the invention with precision appropriate to the technology and without intruding on the prior art."
>
> *Verve LLC vs. Crane Cams Inc.*, 65 USPQ2d 1051, 1054 (Fed. Cir. 2002); emphasis added.

Indeed, the term "substantially" is ubiquitous in patent claims and has long been approved by the Federal Circuit and its predecessor court. *Andrew Corp.* at 2012. Therefore, claim language including "terms of degree" does not automatically render the claim indefinite. Rather, terms of degree are acceptable so long as one of ordinary skill in the art would be apprised of the scope of the claim. MPEP 2173.05(b).

In order to determine whether one of ordinary skill in the art would understand a term of degree in a claim, one should first assess whether the specification "provides some standard for measuring that degree". Should such a standard be provided, the claims meet the requirements of 35 U.S.C. § 112, second paragraph. *Seattle Box Co., Inc. v. Industrial Crating & Packing, Inc.*, 221 USPQ 568, 574 (Fed. Cir. 1984).

Only where the specification does not provide some standard for measuring the degree of a relative term, would a further inquiry be required. Even in such circumstances, the claims are still definite so long as one of ordinary skill in the art would nevertheless be reasonably apprised of the scope of the invention in view of the knowledge in the art. *Seattle Box Co.* at 574; MPEP 2173.05(b). In this case, both the detailed measurement standards set forth in the specification and the knowledge in the art support the definiteness of the pending claims.

Those of ordinary skill in the art would, in light of the detailed guidance in the specification and the knowledge in the biotechnological arts, understand "binds to substantially the same epitope" to mean "antibodies of defined epitope-specificity" or "cross-reactive antibodies" (specification at page 13, lines 15-20). The specification explains in detail that such 2C3 cross-reactive antibodies recognize, bind to or have immunospecificity for substantially or essentially the same epitopic site as 2C3, meaning that the antibodies are able to "effectively compete" with 2C3 for binding to VEGF (specification at page 14, lines 19-27).

The intrinsic evidence, including the detailed guidance in the specification and the successful execution of antibody competition assays to identify anti-VEGF antibodies that bind to substantially the same epitope (Example I, Table 1), coupled with the knowledge of those of ordinary skill in the art, clearly meet the "standard for measuring" required to render words of degree acceptable under 35 U.S.C. § 112, second paragraph. *Seattle Box Co.* at 574.

The extrinsic evidence also supports Appellants' position. For example, the definitive text *Antibodies: A Laboratory Manual* (Eds. Harlow & Lane, Cold Spring Harbor Laboratory, pp 567-569, 1988; **Exhibit E**) describes antibody competition assays in essentially the same manner as the specification (see **Exhibit E** at pages 567, 569 and the specification at pages 13-19).

Moreover, the phrase "binds to substantially the same epitope as the monoclonal antibody..." routinely appears in the claims of issued U.S. patents (see **Exhibit F**, U.S. Patent No. 6,107,049, "the '049 patent"). Claim 4 of the '049 patent recites an anti-PSA antibody that "binds to substantially the same epitope as the monoclonal antibody produced by the cell line ATCC HB-12337 or HB-12338", *i.e.*, the same form of definition as in the presently rejected claims. The present claims must therefore be sufficiently definite. 35 U.S.C. § 282; *Biovail Corp. International vs. Andrx Pharmaceuticals Inc, supra.*

For the foregoing reasons, claims 5-10, 12-23, 29, 30, 42, 47 particularly point out and distinctly claim the invention. In addition, claims 43, 44 and 45 each recite further features of the invention, as supported by the specification and readily understood in the art, and therefore impart additional clarity to these particular claims.

3. Effectively Competing

Claims 52-54 are rejected on the basis that the recitation "effectively competes with" renders the metes and bounds of the claims unclear. Claims 5-23, 29, 30, 42-45 and 47-51 are *prima facie* free from this rejection, as they do not include the term "effectively competes with". As to the rejection of claims 52-54, the clarity of this language is shown by the '758 patent, issued from same specification (**Exhibit D**). In addition, the record shows that the term "effectively competes with" renders the metes and bounds of the claims clear.

The specification explains that antibodies that "bind to substantially the same epitope" are antibodies that are able to "effectively compete with 2C3 for binding to VEGF" (specification at page 14, lines 19-27). Thus, the term "effectively competing" is equally well understood in the art, as explained above, and as further exemplified by standard texts describing antibody competition, such as **Exhibit E.**

Moreover, the specification includes working examples of successful assays in which anti-VEGF antibodies that "effectively compete" with each other "for binding to VEGF" are identified. Notably, Example I describes a panel of anti-VEGF antibodies, two groups of which are identified as antibodies that "effectively compete for binding to VEGF" (specification at pages 214-215, Table 1). The specification thus provides qualitative and quantitative guidance as to "how much effectiveness is required in order to meet the limitations of the claim", as sought by the final Action at page 3.

Claims 52-54 therefore describe the invention with precision appropriate to the technology, without intruding on the prior art, and are properly supported by a specification and knowledge in the art that renders the claims sufficiently definite. *Andrew Corp.* at 2013; *Seattle Box Co.* at 574.

For the foregoing reasoning, the rejections under 35 U.S.C. § 112, second paragraph are in error and should be reversed.

C. Claims 5-23, 29, 30, 42-45 and 47-54 are Supported by an Enabling Specification as Required by 35 U.S.C. § 112, First Paragraph

Claims 5-23, 29, 30, 42-45 and 47-54 are rejected under 35 U.S.C. § 112, first paragraph as allegedly not been supported by an enabling specification (first Action at Item 3; final Action at Item 4). In particular, as the specification allegedly does not reasonably enable antibodies that binds to substantially the same epitope as 2C3 (first Action bridging pages 2-3), as there is no

disclosure as to how to screen for antibodies that bind to such an epitope (first Action at page 3), and as there is no guidance in the specification to delineate what is encompassed by "effectively competes" (final Action at page 3).

Claims 11 and 48 are *prima facie* free from this rejection as they do not, either directly or indirectly, include any of the language that forms the basis of the rejection[4]. As to claims 5-10, 12-23, 29, 30, 42, 47, the rejection is overcome as one of ordinary skill in the art would be able to make and use the claimed invention without undue experimentation in light of the present disclosure and the ordinary technical ability in the art. Claims 52-54 and claims 43-45 are also fully enabled by the specification on these and additional grounds.

1. Counterpart Issued U.S. Patents

Appellants have highlighted on the record the patenting of three applications with the same claim language, issued from the same specification, and pointed out that this is *prima facie* evidence of enabling support for the presently claimed invention ('221, '219 and '758 patents[2,3] of **Exhibit B**, **Exhibit C** and **Exhibit D**). 35 U.S.C. § 282; *Biovail Corp. International vs. Andrx Pharmaceuticals Inc, supra.*

The final Action takes the position that "every case is treated on its own merits and at this time the present claims are being examined on their own merits. The prosecution history of other cases is not considered to have a bearing on the prosecution of this instant case" (final Action at page 4). This position is legally incorrect.

First, as the present application and the '221, '219 and '758 patents each have the same specification, were filed at the same time, claim priority to the same provisional application, and as the claim language at issue is the same, the merits are the same. Second, Federal Circuit case

[4]The first Action agreed that subject matter of the scope of claims 11 and 48 was adequately enabled.

law mandates that the prosecution history of the three related patents must have a bearing on the prosecution of this application, particularly as these four cases were derived from the same initial application:

> "When multiple patents derive from the same initial application, the prosecution history regarding claim limitation in any patent that has issued applies with equal force to subsequently issued patents that contain same claim limitation".
>
> *Biovail Corp.* at 1816.

As the merits are the same and have already been decided in favor of issuance, and as the prosecution history of the '221, '219 and '758 patents is *prima facie* relevant to this application, the rejection is improper and overcome. 35 U.S.C. § 282; *Biovail Corp.*

2. The Claims are Enabled

Aside from issuance of the '221, '219 and '758 patents with the same claim language and specification, the record shows that claims 5-10, 12-23, 29, 30, 42, 47, claims 52-54 and claims 43-45, as well as claims 11 and 48, are enabled by the specification.

The specification more than reasonably enables antibodies that bind to substantially the same epitope as 2C3, provides guidance and working examples of antibodies that effectively compete for binding to VEGF, and provides detailed disclosure as to how to screen for antibodies in accordance with the claimed invention. Moreover, there is a high level of technical skill in the art regarding competing antibodies, as evidenced by published articles and issued U.S. patents.

The specification provides in-depth technical instructions concerning the identification of antibodies that "bind to substantially the same epitope" or "effectively compete" with 2C3 for binding to VEGF (specification at pages 13 and 14), including the technical steps for a range of

assays, the proper controls and the quantitative determinations applicable to the identification of competitive antibodies (specification at pages 14-19).

In the quantitative guidance, the specification teaches how to establish the "control high values" and "control low values", within which antibody competition can be assayed (specification at page 16, lines 19-25). Competitive antibodies are identified as those that cause a significant reduction in binding of the reference antibody, 2C3, to the target antigen, VEGF (specification at page 16). Quantitative values for significant, reproducible and consistently observed reductions in binding are provided in the specification (*e.g.*, bridging pages 16-17) and are related to the actual data in the working examples (Example I; Table 1; specification at page 18, lines 5-10).

Example I of the specification demonstrates the actual application of a competitive ELISA in defining the epitope specificity of a panel of anti-VEGF antibodies. These competitive binding studies resulted in the identification of two groups of cross-blocking antibodies (specification pages 214-215, and summarized in Table 1), such that the GV39M and 11B5 antibodies, and the 3E7 and 7G3 antibodies, effectively competed for binding to VEGF and thus bound to substantially the same epitope (specification at page 214, Table 1, epitope groups 1 and 2).

These data in the specification clearly show, as of the priority date of the present application, the successful application of antibody competition assays between anti-VEGF antibodies in the identification of antibodies that bind to substantially the same epitope and that compete for binding to VEGF. These working examples, coupled with the detailed guidance in the specification, provide intrinsic evidence of enabling support for the claims.

In addition, significant extrinsic evidence is available that further supports patentability. The definitive antibody text of **Exhibit E** shows that antibody competition assays were routinely practiced in the art prior to, and around the time of, Appellants' effective filing date. Note the correspondence between the enabling details in the present specification (*e.g.*, pages 13-19) and the standard text in the art (**Exhibit E** at pages 567, 569). Issuance of U.S. patents in which the antibodies in the claims are defined using the term "binds to substantially the same epitope" (**Exhibit F**) provides further evidence of the technical ability of a skilled artisan to practice the claimed invention without undue experimentation in light of the disclosure. 35 U.S.C. § 282; *Biovail Corp.*

In maintaining the rejection as applied to "substantially the same epitope", the final Action takes the position that knowledge of the amino acid sequence of the epitope is required to enable the invention (final Action at page 3). However, such a position has no basis in the plain language of the claims and is significantly at odds with the teaching in the specification and the knowledge of those of ordinary skill in the art (exemplified by **Exhibit E** and **Exhibit F**).

As to those aspects of the rejection concerning to "effectively competes", the final Action at page 3 indicates that the competition studies in the specification "allow for the determination of competing for binding to the antigen". As such a determination meets the requirement of the claim, this is clear evidence of enabling support. The Action's return to knowledge of the epitope's sequence is irrelevant, as this is not required to practice the invention as claimed.

Despite agreeing that the studies in the specification "allow for the determination of competing for binding to the antigen", the final Action still alleges that "one of skill in the art would be forced into undue burden to determine 'effectively competes with 2C3 for binding to VEGF'". The contradiction is evident. The teaching in the specification, complemented by the

successful studies in the working examples, provides the guidance required to identify an antibody that effectively competes with 2C3 for binding to VEGF.

The final Action attempts to maintain the enablement rejection in the face of the data in the specification, which actually identifies two groups of effectively competing antibodies, by taking the position that the groups of antibodies were "arbitrarily assigned" (final Action at page 3). Although the word "arbitrarily" is used in the specification ("GV39M and 11B5 were *arbitrarily* assigned to epitope group 1, while 3E7 and 7G3 were assigned to epitope group 2"), there is nothing arbitrary regarding the competition studies, only the terminology. Rather than "groups 1 and 2", the competing antibodies could have been arbitrarily assigned to "groups 2 and 1"; or arbitrarily assigned to "groups A and B", "groups X and Y" or "groups Tampa Bay and Oakland". The arbitrary choice of terminology does not indicate a lack of enablement.

For the foregoing reasons, claims 5-10, 12-23, 29, 30, 42, 47, and claims 52-54, are more than adequately enabled by the specification. Each of claims 43, 44 and 45, which recite further features taught in the specification, benefit from the additional enabling teaching and are also in condition for allowance.

Accordingly, the rejection under 35 U.S.C. § 112, first paragraph is in error and should be reversed.

IX. CONCLUSION

In view of the foregoing reasoning, Appellants submit that the rejections are unwarranted and respectfully request that the Board of Patent Appeals and Interferences reverse the rejections of claims 5-23, 29, 30, 42-45 and 47-54. More particularly, that the Board find claims 5-23, 29, 30, 42-45 and 47-54 to be definite under 35 U.S.C. § 112, second paragraph; and find claims 5-23, 29, 30, 42-45 and 47-54 to be enabled under 35 U.S.C. § 112, first paragraph. In

view of the record to date, and the lack of patentably distinct subject matter, Appellants further respectfully request that the Board of Patent Appeals and Interferences direct the Examiner to issue the application with claims 1-54, currently pending in the case.

Respectfully submitted,

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